Economic Evaluation of Pneumococcal Vaccines for Adults Aged Over 50 Years in Belgium: Supporting information

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Abstract

Streptococcus pneumoniae causes a high disease burden including pneumonia, meningitis and septicemia. Both a polysaccharide vaccine targeting 23 serotypes (PPV23) and a 13-valent conjugate vaccine (PCV13) are indicated for persons aged over 50 years. We developed and parameterized a static multi-cohort model to estimate the incremental cost-effectiveness and budget-impact of these vaccines at different uptake levels. Using three different vaccine efficacy scenarios regarding non-invasive pneumococcal pneumonia and extensive uni- and multivariate sensitivity analyses, we found a strong preference for PPV23 over PCV13 in all age groups at willingness to pay levels below €300 000 per quality adjusted life year (QALY). PPV23 vaccination would cost on average about €83 000, €60 000 and €52 000 per QALY gained in 50-64, 65-74 and 75-84 year-olds, whereas for PCV13 this is about €171 000, €201 000 and €338 000, respectively. Strategies combining PPV23 and PCV13 vaccines were most effective but generally less cost-effective. When assuming a combination of increased duration of PCV13 protection, increased disease burden preventable by PCV13 and a 75% reduction of the PCV13 price, PCV13 could become more attractive in <75 year-olds, but would remain less attractive than PPV23 from age 75 years onwards. These observations are independent of the assumption that PPV23 has 0% efficacy against non-invasive pneumococcal pneumonia. Pneumococcal vaccination would be most cost-effective in Belgium, when achieving high uptake with PPV23 in 75-84 year olds, as well as by negotiating a lower market-conform PPV23 price to improve uptake and cost-effectiveness.

Introduction

The bacterial pathogen *Streptococcus pneumoniae* is responsible for a high disease burden and is a major cause of community acquired pneumonia (CAP), meningitis and septicaemia in the elderly. Invasive pneumococcal disease (IPD) is defined as the isolation or detection of *S. pneumoniae* from a normally sterile site, most commonly blood, pleural fluid or cerebrospinal fluid. Non-invasive pneumococcal pneumonia (non-IPP) is less severe but much more frequent than invasive pneumococcal pneumonia. Cases may be hospitalized or only seen in an outpatient visit depending on severity, co-morbidities, age and local policies for admissions.

There are two types of pneumococcal vaccines indicated for the elderly. Since the 1990s, polysaccharide pneumococcal vaccines (PPV) are available. The current PPV vaccine, PPV23, targets 23 serotypes, is licensed in Belgium since 1995 and has been recommended for all elderly $\geqslant$65 years of age in Belgium by the Superior Health Council (CSS/HGR) around the same time. However, the uptake of PPV23 has always been low in this group. Pneumococcal conjugate vaccines (PCV) are available in Europe since 2001. Only the 13-valent PCV (PCV13) has been approved for adults in 2011 against invasive pneumococcal disease and in 2015 against all pneumococcal pneumonia.

PPV23 and PCV13 differ in the number of serotypes covered, the corresponding proportion of pneumococcal disease that they prevent, the type of immunity that is conferred and the price. In addition, the distribution of circulating PCV13 and PPV23 serotypes changed markedly in recent years as a result of universal PCV vaccination of infants (indirect effect or herd immunity through the subsequent use of PCV7, PCV13 and now PCV10 in infants)[1,2]. Overall pneumococcal disease rates in elderly have decreased over time in most settings as a net result of a decrease in disease caused by PCV13 serotypes, though a gradual increase in disease caused by non-PCV13 serotypes has been observed. The decision on which vaccine (and schedule) should be preferred in the elderly thus partly depends on the indirect effects of the infant PCV vaccination.

The research presented in the main article addresses an economic evaluation, adopting a health care payer's perspective. The costs and benefits of different vaccination strategies are compared with each other, including the current situation of low PPV23 vaccination coverage in the elderly. The considered vaccination strategies involve the administration of PPV23 alone, PCV13 alone, PCV13 followed by PPV23, different options for revaccination and different uptake levels (ranging 20-60%) in adults over 50 years. The main research questions are: What is the clinical impact of the vaccination strategies in terms of incremental number of hospitalizations, outpatient cases, fatalities and long term sequelae due to pneumococcal disease? What is the (incremental) cost-effectiveness of the vaccination strategies compared to each other? What is the budget impact of the vaccination strategies?

This study was conducted as a Health Technology Assessment (HTA) for the Belgian Health Care Knowledge Centre (KCE) to assist policy making in Belgium[3]. The full text of the report can be found here. In this supplementary file, we present more details on the modeling results and inputs. A general study overview and the primary results are described in the main text.

Contents

Appendix A

Estimated burden of disease and costs in Belgium by *S. pneumoniae* in 2016.

This supplement presents the predicted burden of disease in Belgium of *S. pneumoniae* in 2016 with low PPV23 vaccine uptake (0.79% for 50-64 years, 2.46% for 65-74 year, 3.01% for 75-84 years and 2.48% for 85-105 years). We estimated to attain 5905 hospitalizations due to *S. pneumoniae* (with 3606 additional patients treated in ambulatory care), about 428 deaths and 4161 QALYs lost. The health care costs for treatment amount to about €33.7 million. The number of fatalities, and particularly those of pneumonia, is higher in older age groups, despite the decreasing size of each age group with increasing age. The number of hospitalizations and especially outpatients decline in the more advanced age groups, and this explains also the decreasing trend in costs by age group. More details can be found in Table A.1.

Table A.1: Estimated burden of disease and costs in 2016 in Belgium related to *S. pneumoniae* in adults 50 years and older. Results presented as the median of 1000 simulations, rounded to the nearest unit.

Age	**50-64 years**	**55-74 years**	**75-84 years**	**85-105 years**	**Total**
Age group size	2 233 358	1 022 444	720 255	288 423	4 264 480
Cases invasive pneumococcal pneumonia	275	224	228	199	926
Cases meningitis, total	29	11	12	10	62
Cases other invasive pneumococcal diseases	27	23	23	20	92
Cases hospitalized non-invasive pneumococcal pneumonia	1431	1169	1188	1036	4824
Total number of hospitalizations	1762	1427	1451	1265	5905
Cases outpatient non-invasive pneumococcal pneumonia	1517	778	822	489	3606
Cases meningitis, with long term hearing loss	3	1	1	1	6
Cases meningitis, with long term neurological sequelae	3	1	1	1	6
Deaths pneumococcal pneumonia	74	77	109	138	398
Deaths meningitis	4	1	3	5	13
Deaths other invasive pneumococcal diseases	4	4	4	5	17
Total number of deaths	82	82	116	147	428
Quality adjusted life years lost	1816	1078	802	465	4161
Quality adjusted life years lost (discounted)	1535	978	761	454	3727
Total direct health care cost in €	13 336 267	9 339 376	7 039 081	3 991 872	33 706 596
Total direct health care cost in € (discounted)	12 328 033	9 137 858	6 940 564	3 954 000	32 360 455

Appendix B

Avoided burden and cost-effectiveness

This supplement presents more details on the estimated cost-effectiveness and avoided burden of disease of vaccination scenarios for different age groups. We present the incremental results of each vaccination strategy comparing to the current situation or other scenarios. First, we present results based on the assumption that both vaccines have baseline efficacy against non-IPP for age groups 50-64 years, 65-74 years and 75-84 years (Table B.2-B.4). Next, we present the predicted avoided burden and costs of scenarios that are affected by the assumption that PPV23 has no efficacy against non-IPP (Table B.5-B.7). Details on the vaccine scenarios can be found in Table B.1.

Table B.1: Vaccination strategies defined by vaccine choice, schedule and uptake in different age groups.

Scenario	**50-64 years**	**55-74 years**	**75-84 years**	**85-105 years**
Current situation (yearly means of the 2004, 2008 and 2013 five year accumulated uptake)	0.79% PPV23	2.46% PPV23	3.01% PPV23	2.48% PPV23
PPV23 (1)	25% PPV23	50% PPV23	60% PPV23	40% PPV23
PCV13 (2)	25% PCV13	50% PCV13	60% PCV13	40% PCV13
PCV13 + PPV23 (3)	(1) + (2)	(1) + (2)	(1) + (2)	(1) + (2)
PPV23 + revaccination	(1) + 15% PPV23 after 5 year	(1) + 25% PPV23 after 5 year	(1) + 25% PPV23 after 5 year	(1) + 20% PPV23 after 5 year
PVC13 + revaccination	(2) + 15% PPV23 after 5 year	(2) + 25% PPV23 after 5 year	(2) + 25% PPV23 after 5 year	(2) + 20% PPV23 after 5 year
PCV13 + PPV23 + revaccination	(3) + 15% PPV23 after 5 year	(3) + 25% PPV23 after 5 year	(3) + 25% PPV23 after 5 year	(3) + 20% PPV23 after 5 year

Table B.2: Avoided burden and cost-effectiveness of vaccination in 50-64 year olds (mean (median) based on 1000 simulations, rounded to the nearest unit)

Scenario	**PPV23**	**PCV13**	**PCV13+ PPV23**	**PCV13+ PPV23**	**PCV13+ PPV23**	**PPV23+ revac.**	**PCV13+ revac.**	**PCV13+ PPV23 + revac.**
Reference	**current**	**current**	**current**	**PPV23**	**PCV13**	**PPV23**	**PCV13**	**PCV13+ PPV23**
Meningitis cases	9 (9)	5 (5)	12 (12)	3 (3)	7 (7)	4 (4)	0 (0)	4 (4)
Other IPD cases	9 (9)	6 (6)	13 (13)	4 (4)	7 (7)	5 (5)	1 (1)	5 (5)
Pneumococcal CAP hospitalizations	217 (218)	269 (268)	411 (410)	194 (194)	142 (143)	86 (86)	29 (29)	66 (67)
Outpatient pneumococcal CAP cases	127 (126)	202 (199)	274 (270)	146 (144)	71 (70)	28 (28)	17 (17)	16 (15)
Deaths meningitis	1 (1)	1 (1)	2 (2)	0 (0)	1 (1)	1 (0)	0 (0)	0 (0)
Deaths other IPD	1 (1)	1 (1)	2 (2)	1 (1)	1 (1)	1 (1)	0 (0)	1 (1)
Pneumococcal CAP deaths	11 (11)	13 (13)	21 (20)	9 (9)	8 (8)	6 (6)	2 (2)	5 (5)
Total deaths	14 (14)	14 (14)	24 (24)	10 (10)	10 (10)	7 (7)	2 (2)	6 (6)
Undiscounted QALY lost	288 (285)	275 (268)	478 (470)	190 (186)	203 (201)	117 (116)	25 (24)	98 (98)
Discounted QALY lost	239 (237)	227 (222)	395 (388)	156 (153)	168 (167)	93 (93)	19 (19)	78 (78)
Total medical cost undiscounted (€)	2 273 774 (2 304 334)	2 141 852 (2 150 497)	3 758 030 (3 754 478)	1 484 256 (1 487 532)	1 616 178 (1 632 994)	907 389 (917 913)	204 203 (204 526)	753 607 (763 893)
Total medical cost discounted (€)	1 897 853 (1 922 192)	1 814 202 (1 819 553)	3 140 474 (3 130 975)	1 242 621 (1 245 382)	1 326 272 (1 342 424)	662 624 (670 614)	144 029 (144 161)	543 429 (549 124)
Total vaccination costs (administration and purchase) discounted	-21 723 637 (-21 723 637)	-47 457 504 (-47 457 504)	-69 858 085 (-69 858 085)	-48 134 448 (-48 134 448)	-22 400 581 (-22 400 581)	-11 169 539 (-11 169 539)	-24 001 146 (-24 001 146)	-11 169 539 (-11 169 539)
ICER = mean (cost) / mean (QALY)	82 814 (83 728)	201 172 (206 351)	168 879 (171 883)	301 246 (307 561)	125 313 (126 149)	113 132 (113 080)	1 262 175 (1 290 100)	136 910 (136 704)

Table B.3: Avoided burden and cost-effectiveness of vaccination in 65-74 year olds (mean (median) based on 1000 simulations, rounded to the nearest unit)

Scenario	**PPV23**	**PCV13**	**PCV13+ PPV23**	**PCV13+ PPV23**	**PCV13+ PPV23**	**PPV23+ revac.**	**PCV13+ revac.**	**PCV13+ PPV23 + revac.**
Reference	**current**	**current**	**current**	**PPV23**	**PCV13**	**PPV23**	**PCV13**	**PCV13+ PPV23**
Meningitis cases	7 (7)	4 (4)	10 (10)	3 (3)	6 (6)	3 (3)	0 (0)	3 (3)
Other IPD cases	14 (15)	8 (8)	19 (20)	5 (5)	11 (11)	6 (6)	1 (1)	6 (6)
Pneumococcal CAP hospitalizations	342 (344)	349 (351)	575 (574)	232 (229)	226 (227)	101 (102)	16 (15)	78 (79)
Outpatient pneumococcal CAP cases	134 (132)	180 (179)	256 (254)	122 (121)	76 (75)	27 (26)	7 (7)	15 (15)
Deaths meningitis	1 (1)	1 (1)	1 (1)	0 (0)	1 (1)	1 (1)	0 (0)	1 (1)
Deaths other IPD	2 (2)	1 (1)	3 (3)	1 (1)	2 (2)	1 (1)	0 (0)	1 (1)
Deaths pneumococcal CAP hospitalizations	25 (25)	23 (22)	41 (40)	16 (15)	18 (18)	10 (10)	1 (1)	9 (9)
Total deaths	29 (28)	25 (24)	45 (44)	17 (16)	20 (20)	12 (12)	2 (2)	10 (10)
Undiscounted QALY lost	337 (333)	272 (266)	511 (503)	174 (170)	239 (236)	102 (101)	11 (11)	85 (86)
Discounted QALY lost	301 (298)	240 (235)	452 (447)	152 (148)	213 (211)	86 (86)	9 (9)	72 (72)
Total medical cost undiscounted (€)	2 559 386 (2 575 999)	2 268 919 (2 275 051)	4 023 606 (4 014 425)	1 464 220 (1 461 007)	1 754 687 (1 768 112)	703 101 (710 144)	83 592 (81 846)	569 559 (575 383)
Total medical cost discounted (€)	2 340 219 (2 355 593)	2 034 813 (2 042 580)	3 624 245 (3 613 952)	1 284 026 (1 279 330)	1 589 432 (1 602 632)	550 574 (556 219)	59 156 (57 756)	442 472 (446 616)
Total vaccination costs (administration and purchase) discounted	-19 545 248 (-19 545 248)	-43 107 470 (-43 107 470)	-63 617 697 (-63 617 697)	-44 072 449 (-44 072 449)	-20 510 227 (-20 510 227)	-7 978 159 (-7 978 159)	-17 143 496 (-17 143 496)	-7 978 159 (-7 978 159)
ICER = mean (cost) / mean (QALY)	57 212 (57 716)	171 344 (174 491)	132 590 (134 364)	281 970 (288 510)	88 929 (89 579)	86 217 (86 564)	1 954 873 (2 005 960)	104 198 (104 021)

Table B.4: Avoided burden and cost-effectiveness of vaccination in 75-84 year olds (mean (median) based on 1000 simulations, rounded to the nearest unit)

Scenario	**PPV23**	**PCV13**	**PCV13+ PPV23**	**PCV13+ PPV23**	**PCV13+ PPV23**	**PPV23+ revac.**	**PCV13+ revac.**	**PCV13+ PPV23 + revac.**
Reference	**current**	**current**	**current**	**PPV23**	**PCV13**	**PPV23**	**PCV13**	**PCV13+ PPV23**
Meningitis cases	9 (9)	4 (4)	11 (11)	2 (2)	7 (7)	1 (2)	0 (0)	1 (1)
Other IPD cases	18 (18)	8 (8)	22 (22)	4 (4)	14 (14)	3 (3)	0 (0)	3 (3)
Pneumococcal CAP hospitalizations	422 (423)	151 (159)	505 (501)	83 (78)	354 (350)	47 (47)	4 (2)	39 (39)
Outpatient pneumococcal CAP cases	161 (159)	51 (53)	188 (185)	27 (21)	137 (132)	11 (11)	2 (0)	8 (7)
Deaths meningitis	3 (3)	1 (1)	3 (3)	1 (1)	2 (2)	1 (1)	0 (0)	0 (0)
Deaths other IPD	3 (3)	1 (2)	4 (4)	1 (1)	3 (3)	1 (1)	0 (0)	1 (1)
Deaths pneumococcal CAP	45 (45)	18 (18)	56 (55)	10 (10)	38 (38)	6 (6)	1 (0)	6 (6)
Total deaths	51 (51)	20 (21)	63 (63)	12 (12)	43 (42)	8 (8)	1 (1)	7 (7)
Undiscounted QALY lost	297 (294)	115 (118)	356 (353)	59 (58)	241 (239)	34 (34)	3 (2)	30 (30)
Discounted QALY lost	277 (275)	105 (109)	330 (328)	54 (52)	225 (223)	30 (30)	2 (2)	26 (26)
Total medical cost undiscounted (€)	2 190 270 (2 199 671)	804 301 (846 006)	2 610 605 (2 604 577)	420 335 (401 840)	1 806 304 (1 799 159)	238 671 (240 687)	19 739 (10 013)	201 883 (204 520)
Total medical cost discounted (€)	2 037 593 (2 048 091)	720 635 (759 370)	2 400 162 (2 394 913)	362 570 (345 028)	1 679 527 (1 668 893)	189 543 (191 253)	16 478 (7 106)	159 723 (162 038)
Total vaccination costs (administration and purchase) discounted	-16 465 506 (-16 465 506)	-36 383 438 (-36 383 438)	-53 721 416 (-53 721 416)	-37 255 910 (-37 255 910)	-17 337 978 (-17 337 978)	-4 497 254 (-4 497 254)	-9 663 716 (-9 663 716)	-4 497 254 (-4 497 254)
ICER = mean (cost) / mean (QALY)	52 147 (52 606)	338 159 (325 811)	155 395 (156 659)	688 486 (701 802)	69 655 (70 189)	143 642 (143 834)	4 058 817 (6 148 401)	165 978 (165 633)

Table B.5: Avoided burden and cost-effectiveness of vaccination in 50-64 year olds focusing on outcomes differentially affected by assuming 0% PPV23 protection against non-IPP. Mean (and median) values are presented based on 1000 simulations, rounded to the nearest unit.

Scenario	**PPV23**	**PCV13+ PPV23**	**PCV13+ PPV23**	**PCV13+ PPV23**	**PPV23+ revac.**	**PCV13+ PPV23 + revac.**
Reference	**current**	**current**	**PPV23**	**PCV13**	**PPV23**	**PCV13+ PPV23**
Pneumococcal CAP hospitalizations	91 (92)	340 (340)	249 (249)	72 (73)	53 (54)	48 (48)
Outpatient pneumococcal CAP cases	0 (0)	202 (199)	202 (199)	0 (0)	0 (0)	0 (0)
Deaths pneumococcal CAP	6 (6)	18 (18)	12 (11)	5 (5)	4 (4)	4 (4)
Total deaths	9 (9)	21 (21)	13 (12)	7 (7)	6 (6)	5 (5)
Undiscounted QALY lost	185 (186)	420 (415)	235 (229)	145 (146)	94 (94)	85 (85)
Discounted QALY lost	153 (154)	347 (342)	194 (188)	120 (120)	75 (75)	67 (68)
Total medical cost undiscounted (€)	1 544 001 (1 560 490)	3 350 223 (3 357 728)	1 806 222 (1 812 282)	1 208 371 (1 221 041)	715 758 (724 050)	646 305 (653 404)
Total medical cost discounted (€)	1 198 029 (1 211 728)	2 749 371 (2 754 083)	1 551 342 (1 552 508)	935 169 (946 770)	504 164 (510 044)	454 701 (459 934)
ICER = mean (cost) / mean (QALY)	134 520 (133 754)	193 672 (195 888)	240 215 (247 945)	179 448 (178 542)	143 114 (142 471)	159 132 (158 365)

Table B.6: Avoided burden and cost-effectiveness of vaccination in 65-74 year olds focusing on outcomes differentially affected by assuming 0% PPV23 protection against non-invasive CAP. Mean (and median) values are presented based on 1000 simulations, rounded to the nearest unit

Scenario	**PPV23**	**PCV13+ PPV23**	**PCV13+ PPV23**	**PCV13+ PPV23**	**PPV23+ revac.**	**PCV13+ PPV23 + revac.**
Reference	**current**	**current**	**PPV23**	**PCV13**	**PPV23**	**PCV13+ PPV23**
Pneumococcal CAP hospitalizations	142 (145)	461 (463)	319 (320)	112 (114)	62 (63)	56 (57)
Outpatient pneumococcal CAP cases	0 (0)	180 (179)	180 (179)	0 (0)	0 (0)	0 (0)
Deaths pneumococcal CAP	15 (15)	35 (34)	20 (19)	12 (12)	8 (8)	7 (7)
Total deaths	19 (19)	40 (39)	21 (20)	15 (15)	10 (10)	9 (9)
Undiscounted QALY lost	221 (221)	445 (440)	224 (219)	173 (173)	82 (83)	74 (75)
Discounted QALY lost	197 (197)	393 (390)	197 (192)	154 (154)	70 (70)	63 (63)
Total medical cost undiscounted (€)	1 407 644 (1 422 650)	3 370 651 (3 377 205)	1 963 008 (1 964 573)	1 101 732 (1 115 574)	506 897 (513 110)	457 520 (462 632)
Total medical cost discounted (€)	1 231 614 (1 246 499)	2 995 547 (3 003 829)	1 763 934 (1 767 914)	960 734 (973 552)	387 714 (392 483)	349 445 (353 452)
ICER = mean (cost) / mean (QALY)	93 164 (93 035)	154 073 (155 640)	214 884 (220 802)	127 148 (126 935)	108 886 (108 234)	121 233 (120 303)

Table B.7: Avoided burden and cost-effectiveness of vaccination in 75-84 year olds focusing on outcomes differentially affected by assuming 0% PPV23 protection against non-invasive CAP. Mean (and median) values are presented based on 1000 simulations, rounded to the nearest unit

Scenario	**PPV23**	**PCV13+ PPV23**	**PCV13+ PPV23**	**PCV13+ PPV23**	**PPV23+ revac.**	**PCV13+ PPV23 + revac.**
Reference	**current**	**current**	**PPV23**	**PCV13**	**PPV23**	**PCV13+ PPV23**
Pneumococcal CAP hospitalizations	175 (178)	298 (299)	123 (123)	147 (145)	29 (29)	26 (27)
Outpatient pneumococcal CAP cases	0 (0)	55 (53)	55 (53)	4 (0)	0 (0)	0 (0)
Deaths pneumococcal CAP	28 (28)	41 (41)	13 (13)	23 (23)	5 (5)	5 (5)
Total deaths	34 (35)	49 (48)	14 (14)	28 (28)	6 (6)	6 (6)
Undiscounted QALY lost	195 (197)	274 (273)	78 (77)	159 (158)	28 (28)	26 (26)
Discounted QALY lost	182 (183)	253 (252)	71 (70)	148 (147)	24 (25)	22 (22)
Total medical cost undiscounted (€)	1 140 457 (1 153 939)	1 742 765 (1 744 464)	602 308 (605 272)	938 464 (934 312)	166 954 (168 459)	151 503 (152 679)
Total medical cost discounted (€)	1 025 739 (1 040 724)	1 563 189 (1 563 209)	537 451 (541 760)	842 555 (837 547)	130 001 (131 248)	117 838 (118 911)
ICER = mean (cost) / mean (QALY)	85 001 (84 274)	206 160 (206 720)	514 585 (522 877)	111 806 (112 348)	178 542 (177 869)	196 832 (195 995)

Appendix C

Sensitivity analysis

In addition to the exploration of three vaccine efficacy scenarios for non-IPP and a parametric sensitivity analysis based on Monte-Carlo sampling, we also explored model uncertainty though a uni- and multivariate sensitivity analysis. Unless stated otherwise, all results reported in this supplement were obtained with fully parameterized vaccine efficacy against non-IPP for both PCV13 and PPV23. We report results for WTP levels up to €350 000 per QALY gained, so when we say an option is unlikely the most beneficial at any WTP level, it is implied that this is for any WTP level up to €350 000 per QALY.

Univariate sensitivity analysis

In the univariate (or one way) sensitivity of the input parameters on the effectiveness and cost-effectiveness of the different strategies, each assumption was tested while keeping all other parameters fixed. We tested 17 assumptions:

Higher PPV23 protection against non-IPP by assuming the vaccine effectiveness ratio for non-IPP/IPD = 0.77 (instead of baseline 0.55) makes PPV23 vaccination more cost-effective, lowering the WTP level to about €40 000 per QALY for 65-84 year olds. PCV13 containing strategies are no longer the most beneficial over the entire WTP range considered.

Five years of PCV13 protection followed by no protection does not dominate baseline PPV23 protection (with or without revaccination) targeted at 65-84 year olds and 50-64 year olds in those age groups when WTP exceeds €50 000 and €80 000 per QALY, respectively. PCV13 is unlikely to be the most cost-effective option at any WTP level considered.

Minimum duration of PCV13 protection (i.e. 4 years fixed protection followed by rapid waning to no protection at 10 years) and baseline PPV23 protection, provides very similar results to those of the previous scenario.

Maximum duration of PCV13 protection (i.e. 9 years fixed protection followed by slow waning to no protection at 20 years) and baseline PPV23 protection, lowers the WTP level at which strategies with PCV13 are retained in 50-74 year olds to about €250 000 - €275 000 per QALY. In 75-84 year olds, PCV13 is still not included as part of the most beneficial strategies at any WTP level considered.

Age-independent PCV13 efficacy in all ages between 50-84 year old using the constant overall vaccine efficacy as reported in CAPITA and still 0% efficacy in >85 year olds, makes PCV13 unlikely to be the most cost-effective option in any age group at any WTP level considered. While this seems logical for those aged 50-64 years, it may sound counter-intuitive for older age groups. For 65-74 year olds, at a WTP around €350 000 per QALY, there is a clear difference between the baseline result and the result when assuming an age-independent

PCV13 vaccine efficacy. The tilting point of age-dependence is 72 years (average age CAPITA study), meaning that under the age-independence assumption, 65-72 year olds will have a lower PCV13 vaccine efficacy and 73-74 year olds will have a higher PCV13 vaccine efficacy. The 65-72 years however dominate the result of the age category 65-74, meaning that PCV13 scenarios become less attractive when assuming an age-independent PCV13 vaccine efficacy. For 75-84 year olds, the improved efficacy estimate lowers the certainty by which the PPV23-only strategies dominate PCV13 containing strategies over the range of WTP considered. When WTP exceeds €400 000, PCV13+PPV23 with revaccination is the strategy with the highest expected benefits.

Two years of complete PPV23 protection followed by no protection and with baseline PCV13 vaccine protection, requires the WTP to exceed €90 000 for any PPV23 vaccination strategy to become cost effective. PCV13 is unlikely to be the most cost-effective option at any WTP level considered.

Five years of PPV23 protection without waning followed by no protection and with baseline PCV13 vaccine protection, makes PPV23 yet more cost-effective compared to PCV13 for all age groups, and becomes overall more rapidly a more attractive strategy versus the current situation. This is especially the case in the age groups 65-74 and 75-84 years, from a WTP threshold of about €40 000 per QALY. PCV13 containing strategies are unlikely to be preferred in any age group.

Five years of both PCV13 and PPV23 protection without waning followed by no protection is almost identical to the previous change. PPV23 is even more certain to be the most beneficial over the entire WTP range.

Minimum serotype shift with a PCV13 serotype incidence decline of 10% per year, and baseline replacement (76%), makes vaccination options slightly more cost-effective. The age group of 65-84 years remains the most beneficial to subsidize pneumococcal vaccination using PPV23 from about €45 000 per QALY. In 50-64 year olds, vaccination with PPV23 becomes likely beneficial from a WTP of about €70 000, and from about €220 000 with PCV13+PPV23 with revaccination (€200 000 for 65-74 year olds). For 75-84 year olds PCV13 containing strategies are not selected as the most cost-effective.

Maximum serotype shift with a PCV13 serotype incidence decline of 20% per year and baseline replacement (76%), echoes our baseline analyses though slightly less favorable towards vaccination. PPV23 is not likely cost-effective until WTP exceeds about €50 000 - €70 000 per QALY. PCV13 containing options are not likely to be the most cost-effective in any age group.

Quick serotype relapse in which the PCV13 serotype incidence returns to the 2015 value within 7 years, all vaccination options become more attractive, and in particular PCV13 containing and PPV23 revaccination options for <85 year olds. PPV23 with revaccination of 50-84 year olds appears as the most beneficial strategy from WTP of €50 000 - €130 000. Next, PCV13+PPV23 with revaccination of 50-84 year olds tends to be cost-effective from WTP of about €130 000 per QALY. In 75-84 year olds, PCV13+PPV23 with revaccination becomes the most beneficial at WTP >€230 000. Following the introduction of infant PCV10 in other countries, overall IPD did hardly decline though non-PCV10 types increased rapidly, most often driven by a 19A rise. If these trends would continue, overall disease incidence could increase above pre-vaccination levels, as observed in Finland in 2015, five years after PCV10 introduction[4].

Slow serotype relapse with the PCV13 serotype incidence returning to 2015 value within 15 years, all vaccination options become more attractive compared to the default settings, but

less so than in the "quick" relapse scenario described above. The most beneficial PCV13 containing scenario is PCV13+PPV23 with revaccination in the age groups 50-74 year olds (from €175 000). For 75-84 year olds, no PCV13 containing strategies are likely to be the most beneficial at any WTP level considered.

Higher hospitalized pneumococcal pneumonia incidence by doubling the baseline incidence of pneumococcal pneumonia hospitalizations makes PPV23 vaccination of 50-84 year olds likely to be cost-effective at a WTP value of €50 000 per QALY gained. This is especially the case for 75-84 year and 65-84 year old groups from about €25 000 and €30 000 per QALY gained, respectively. In the age groups 50-64 years and 65-74 years, PCV13 containing strategies in combination with PPV23, tend to be the most cost-effective at a WTP per QALY exceeding €200 000 and €160 000, respectively. In 75-84 year olds, a PCV13 containing strategy seems never the most beneficial.

Higher percentage of pneumococcal pneumonia in outpatient CAP (i.e. 27%[5] instead of 10.5%) makes all vaccination options more attractive, especially PPV23. We observed as most optimal with increasing WTP, as with most other scenarios, first the current situation, then PPV23 alone and subsequently with PPV23 revaccination is preferred. Finally from a WTP above €250 000, the most beneficial strategy for the age group 50-74 years is PCV13+PPV23 with revaccination but this is not the case for those over 75 years of age.

PCV13 price reduction analysis shows that 25% to 50% reductions in the price of PCV13 makes little difference to the overall picking order of age groups and strategies. If we assume that PPV23 has 0% efficacy against non-IPP, PCV13 price reductions of 75% do have an effect. In that case, especially the age groups of 50-64 and 65-74 years are more likely to favor PCV13 containing strategies. The minimum WTP level at which PCV13 containing strategies are favored over PPV23 alone when the price is reduced by 25%, 50% and 75% is at about €250 000, €200 000 and €55 000 for 50-64 year olds and at about €250 000, €170 000 and €50 000 for 65-74 year olds. None of these price reductions show the highest expected benefits for a PCV13 containing strategy in 75-84 year olds below a WTP of €250 000 per QALY. In the age group 75-84 years, a price reduction of 75%, and assuming no protection of PPV23 against non-IPP, still only leads to the selection of PPV23 based strategies. The only strategy including a PCV13 component for this age group is PCV13+PPV23 with revaccination having the highest expected net benefits when WTP attains about €250 000 per QALY.

PPV23 price reductions make PPV23 containing strategies more attractive. The current retail price of PPV23 (€28.46 per dose), as modeled throughout this analysis, is higher than in some other countries. For instance in France, the retail price in 2015 was €12.46 per dose. Price reductions are most influential for strategies that use multiple vaccine doses, but the single dose PPV23 strategy remains most cost-effective in 75-84 year olds. The incremental cost-effectiveness of revaccination with PPV23 over single dose PPV23 remains most cost-effective for 65-74 year olds. With a 75% reduction in PPV23 price, the mean ICERs for these strategies, depending on the inclusion or exclusion of an effect on non-IPP, become €20 000 - €37 000 and €37 000 - €48 000 per QALY gained, respectively.

Higher PPV23 vaccine efficacy against IPD (82% versus 56% in the baseline) and non-IPP (43% versus 31% in the baseline), makes all PPV23 containing strategies more attractive. However, the influence of this variation is not very large and there is no change in the relative attractiveness of the different strategies. With this higher efficacy, the ICERs of increased PPV23 uptake for 50-64 year, 65-74 year and 75-84 year decline to about €55 000, €37 000 and €34 000, respectively if PPV23 protects against non-IPP, and €89 000, €61 000,

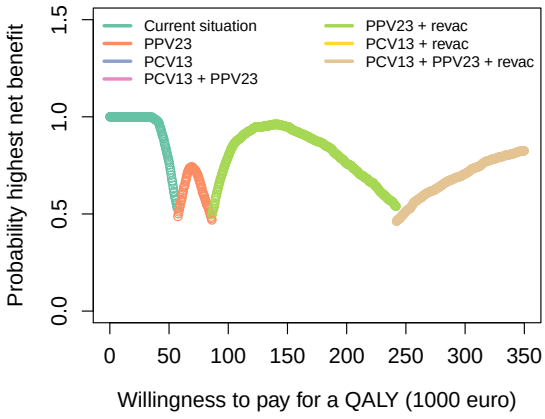
€56 000 if it does not. A 50% PPV23 price reduction would further make these values decline to €33 000, €21 000, €19 000 and €55 000, €37 000, €34 000, respectively.

The price analysis shown in Figure C.1, illustrates the impact of increasing PCV13 price reductions (from top to bottom) for the age group 65-74 year olds. It indicates that from a 75% price cut, single dose PCV13 emerges as the most beneficial option for WTP values around €50 000 - €100 000 per QALY. This is particularly the case when PPV23 is assumed to have 0% efficacy against non-IPP.

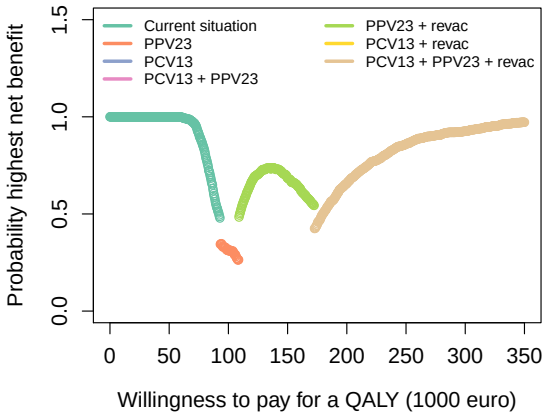
Multivariate sensitivity analysis

In the multivariate sensitivity analyses, we simultaneously varied a number of assumptions and parameter choices discussed in the previous section. Numerous combinations can be made, though we point out some notable aspects in this section.

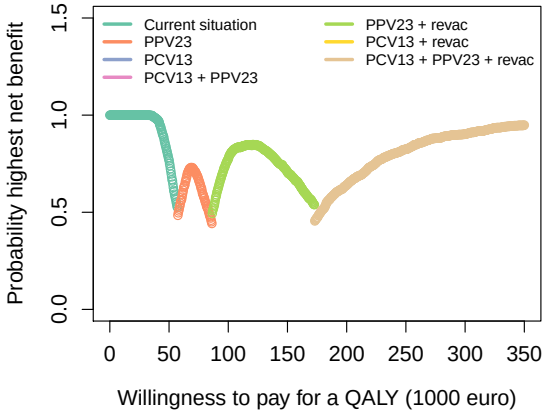
The combination of PCV13 price reductions and a relapse in PCV13 serotypes that are not covered by the PCV10 vaccine from the childhood vaccination program in Belgium could change the prioritization of PPV23 over PCV13 for the ages 50-74 years. This finding is illustrated by a bivariate analysis shown in Figure C.2, showing the impact of increasing PCV13 price reductions (from top to bottom) with maximum duration of PCV13 protection, assuming normal (left hand side) and 50% higher pneumococcal pneumonia incidence (right hand side). Maximum duration of PCV13 protection is defined as 9 years fixed protection followed by slow waning to no protection at 20 years. Figure C.3 shows similar results under the assumption of a minimum duration of PCV13 protection (i.e.4 years fixed protection followed by rapid waning to no protection at 10 years). Both results were obtained assuming that PPV23 has 0% efficacy against non-IPP. These results indicate that from a 50% to 75% price cut, single dose PCV13 can emerge as the most beneficial option for WTP values around €50 000 - €100 000 per QALY gained, especially when we assume PCV13 has a long duration of protection. Under the assumption that PCV13 has a minimum duration of protection, the single PCV13 dose needs to be complemented with PPV23 revaccination to be the most cost-effective. If we simultaneously assume a relapse of PCV13 types in adults, the presence of PPV23 revaccination in the most beneficial options occurs earlier, i.e. for lower WTP values (results not shown).



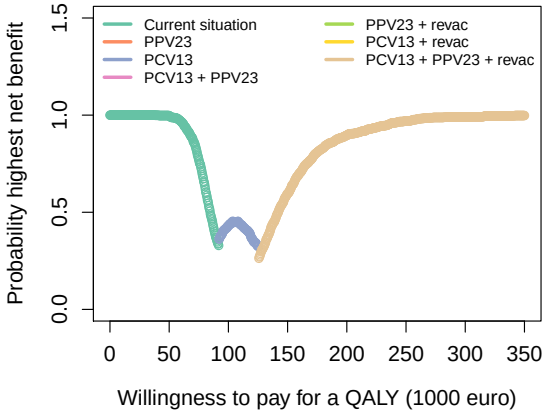
25% PCV13 price reduction



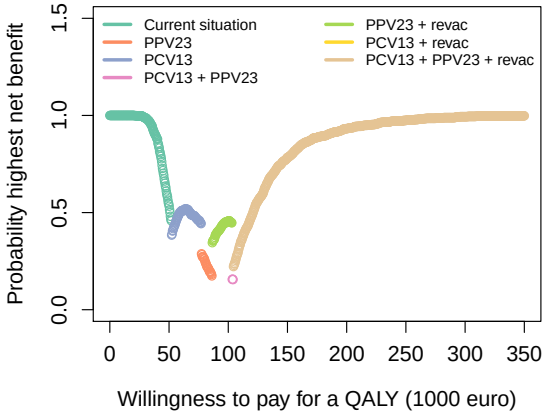
PPV23 provides no non-IPP protection
25% PCV13 price reduction



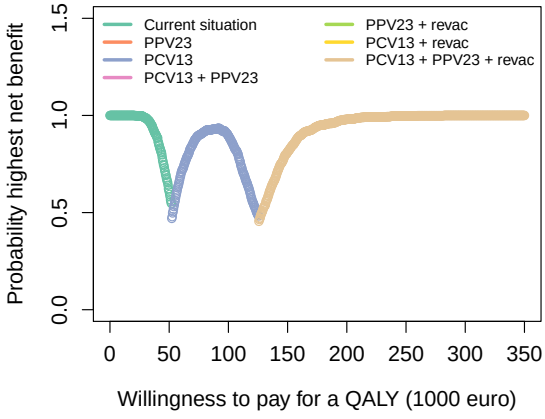
50% PCV13 price reduction



PPV23 provides no non-IPP protection
50% PCV13 price reduction

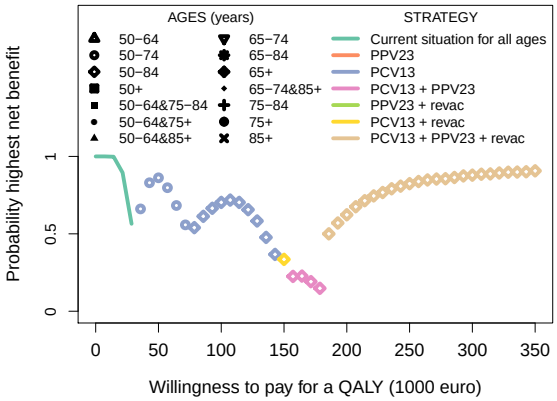


75% PCV13 price reduction

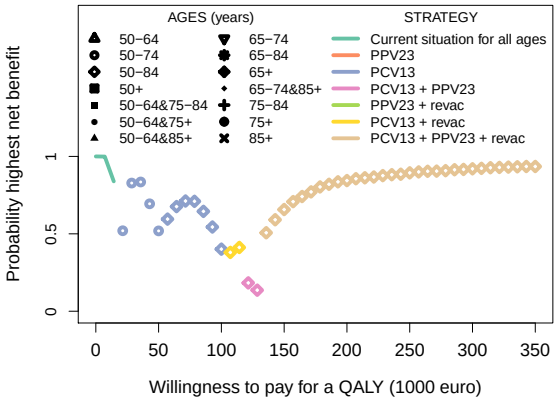


PPV23 provides no non-IPP protection
75% PCV13 price reduction

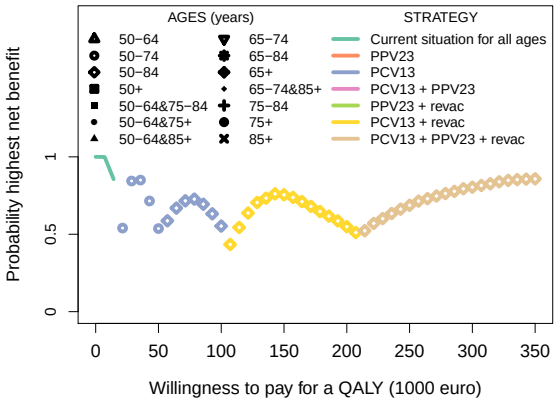
Figure C.1: Cost-effectiveness acceptability frontiers for the 65-74 year olds with increasing PCV13 price reductions, assuming baseline efficacy against non-invasive CAP for both vaccines (left hand side) or assuming PPV23 has 0% efficacy against non-invasive CAP while PCV13 has baseline efficacy (right hand side).



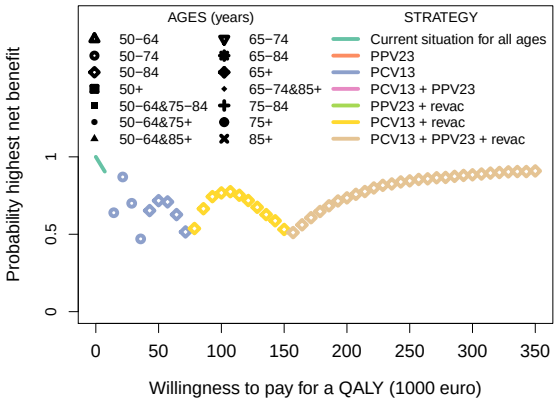
25% PCV13 price reduction



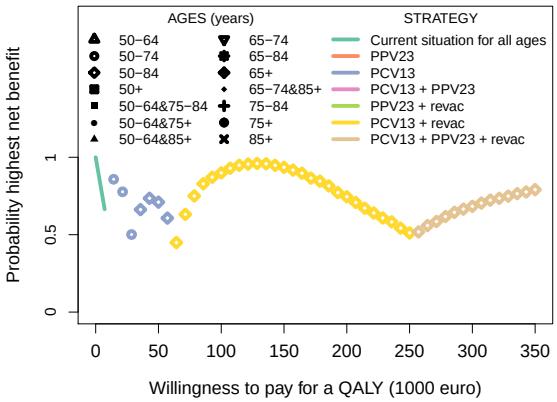
50% higher incidence of pneumococcal pneumonia
25% PCV13 price reduction



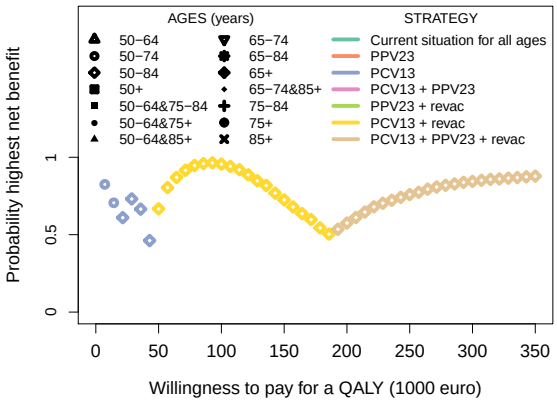
50% PCV13 price reduction



50% higher incidence of pneumococcal pneumonia
50% PCV13 price reduction

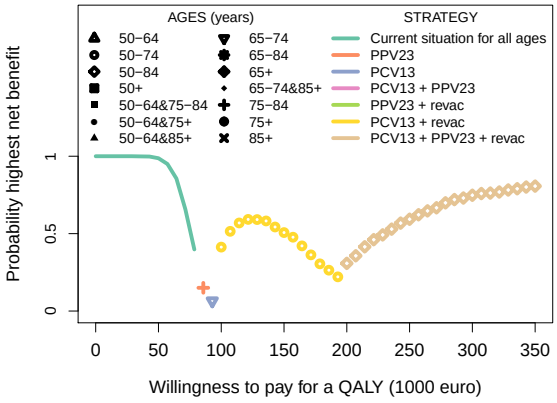


75% PCV13 price reduction

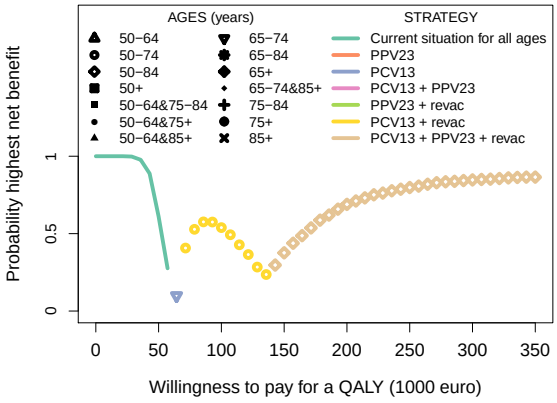


50% higher incidence of pneumococcal pneumonia
75% PCV13 price reduction

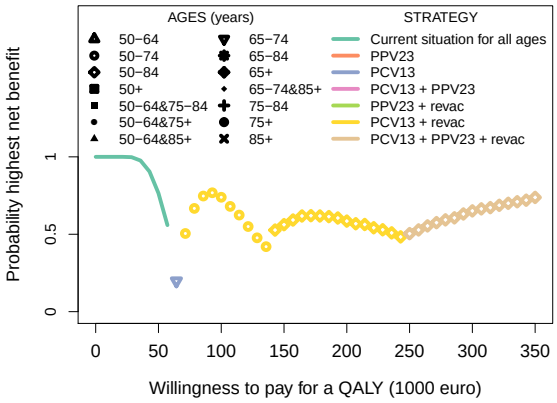
Figure C.2: Cost-effectiveness acceptability frontiers assuming quick serotype relapse and maximum duration of protection for PCV13 with decreasing PCV13 prices, assuming baseline and 50% higher incidence of pneumococcal pneumonia. All results are obtained assuming PPV23 has 0% efficacy against non-invasive CAP while PCV13 has baseline efficacy.



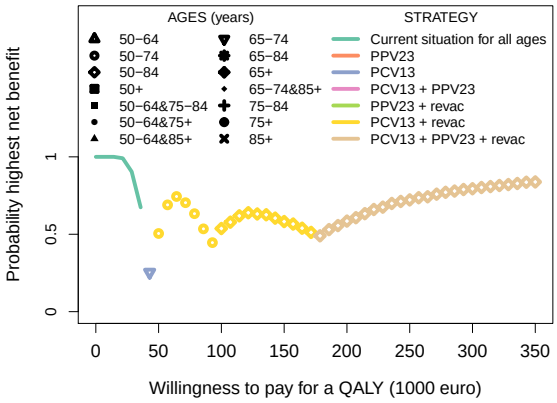
25% PCV13 price reduction



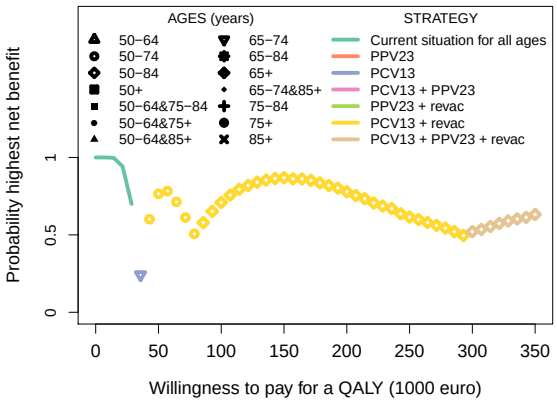
50% higher incidence of pneumococcal pneumonia
25% PCV13 price reduction



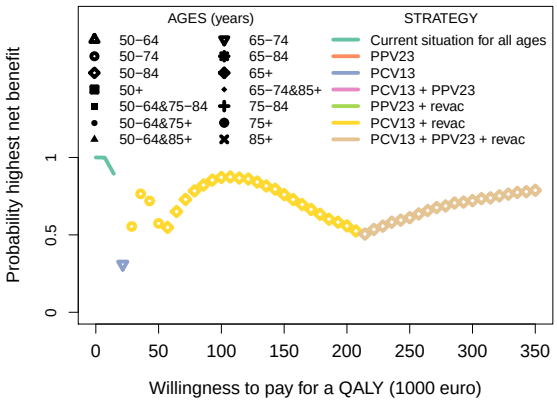
50% PCV13 price reduction



50% higher incidence of pneumococcal pneumonia
50% PCV13 price reduction



75% PCV13 price reduction



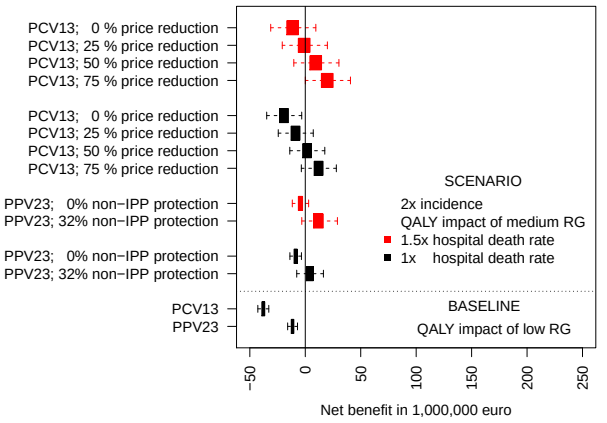
50% higher incidence of pneumococcal pneumonia
75% PCV13 price reduction

Figure C.3: Cost-effectiveness acceptability frontiers assuming quick serotype relapse and minimum duration of protection for PCV13 with decreasing PCV13 prices, assuming baseline and 50% higher incidence of pneumococcal pneumonia. All results are obtained assuming PPV23 has 0% efficacy against non-invasive CAP while PCV13 has baseline efficacy.

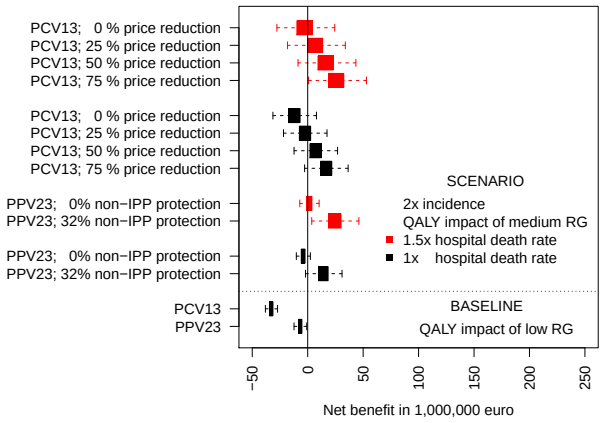
The incidence of pneumococcal pneumonia is most influential in combination with changes in the severity of illness (such as all hospitalization and death rates). The joined impact of these factors is illustrated through the box plots shown in Figure C.4 and C.5. Both figures present the net benefit of the PPV23 and PCV13 vaccination strategy versus the current situation when doubling all incidences and assuming a willingness to pay of €35 000 per QALY gained. In Figure C.5, also a quick serotype relapse scenario is included as a change from the baseline. When the net benefits are positive for a given WTP value, the strategy is cost saving versus the current situation at that particular WTP level. The parametric uncertainty remains fully reflected by the position of the box plot versus 0 in each scenario considered. For ease of reference, we also added the box plots of the baseline settings for the PPV23 and PCV13 scenarios, in which vaccine efficacy against non-IPP is parameterized for both vaccines. When a given box plot is with its average or completely more to the right than another one (say if baseline PPV23 is more to the right than baseline PCV13), that means that the scenario it represents is on average or completely more beneficial. Figure C.4 and C.5 show results for each age group. The >85 year olds can be ignored given the 0% vaccine efficacy for this age group.

Figure C.4 indicates that when PPV23 has some protection against non-IPP, doubling all incidences are sufficient to make PPV23 cost-saving at a WTP of €35 000 per QALY for all age groups <85 years (and more so for the older than the younger age groups), but not if PPV23 has 0% protection against non-IPP. Such savings only occur for PCV13, if the PCV13 price decreases by at least 50%. An increase in the in-hospital death rate by 50% keeps the relative advantage of PPV23 over PCV13 constant in the two youngest age groups, but increases it in 75-84 year olds. Figure C.5 shows that the addition of a quick serotype relapse scenario makes PCV13 in these circumstances clearly preferable to PPV23, except in the 75-84 year olds where PPV23 still yields the highest net benefits.

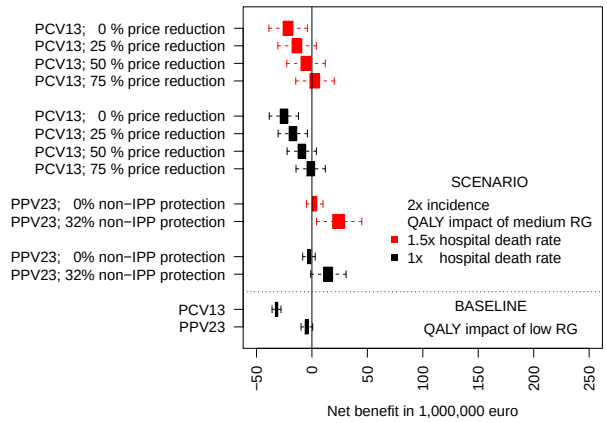
So for PCV13, the combination of vaccine price decreases and an increase in PCV13 non-PCV10 serotypes (i.e. relapse) scenarios is more important to make it preferable to PPV23 than other parameter combinations. If we assume that PPV23 has baseline protection against non-invasive pneumonia, then two by two combinations of price reductions with either a higher pneumonia incidence or higher vaccine efficacy are sufficient to yield net benefits at a WTP of €35 000 per QALY gained in each age group <85 years. However, when we assume PPV23 has 0% protection against non-invasive pneumonia, then price reductions need to be combined with higher incidence estimates, and the influence of vaccine efficacy against invasive pneumonia is less important.



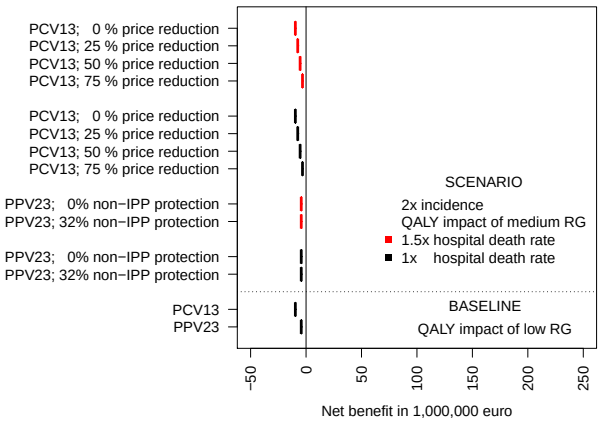
Age group: 50-64 years



Age group: 65-74 years

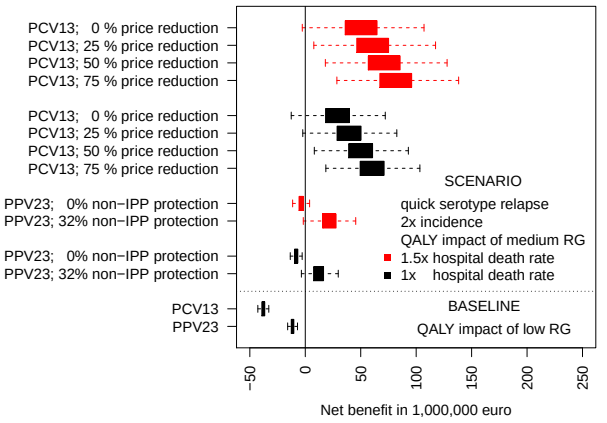


Age group: 75-84 years

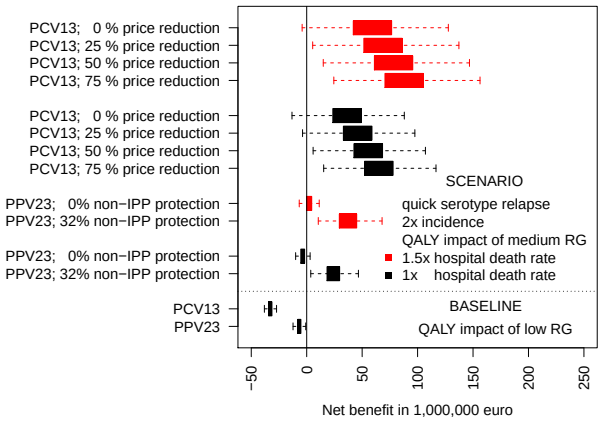


Age group: 85-105 years

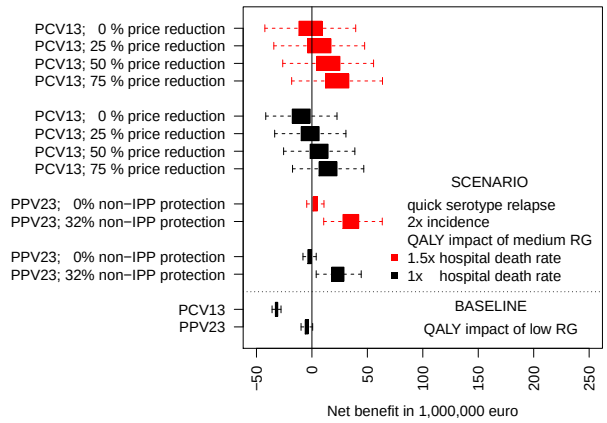
Figure C.4: Net benefit box plots of PPV23 and PCV13 use versus the current situation when doubling all incidences, using QALY impact of the medium risk group, assuming a willingness to pay of 35 000 euro per QALY gained and varying death rate for hospitalized cases. Baseline results at the bottom are obtained with QALY impact of the low risk group.



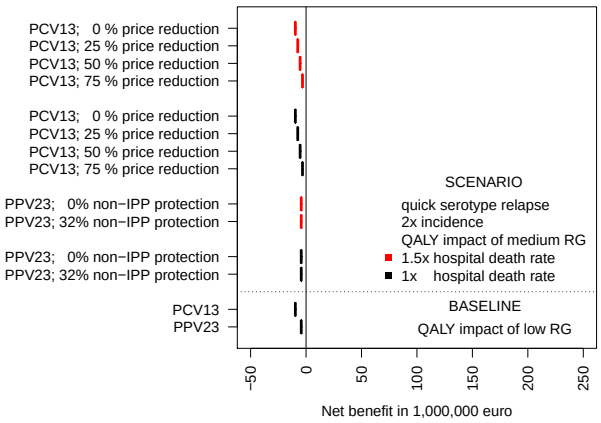
Age group: 50-64 years



Age group: 65-74 years



Age group: 75-84 years



Age group: 85-105 years

Figure C.5: Net benefit box plots of PPV23 and PCV13 use versus the current situation when assuming quick serotype relapse (PCV13 incidence returns to 2015 value within 7 years), doubling all incidences, using QALY impact of the medium risk group, assuming a willingness to pay of 35 000 euro per QALY gained and varying death rate for hospitalized cases. Baseline results at the bottom are obtained with QALY impact of the low risk group.

Appendix D

Budget-impact analysis

The budget-impact of the PPV23 and PCV13 strategy (as defined in Table E.6) versus the current situation is shown in Table D.1, assuming a baseline parameterized efficacy of both vaccines against non-IPP. It shows that the avoided treatment costs (< €10 million for combined ages 50+), benefiting mainly the national health insurer RIZIV/INAMI and patients, are much lower than the required vaccination costs (>€80 million for 50-84 year olds) incurred by the funder of preventive vaccination, expected to be mainly regional governments (Flanders, Wallonia, Brussels) and patients. This results in a low (<11%) return on investment, and net costs in excess of €72.9 million for 50-84 year olds. There is little difference between 5 or 10-year time spans because the change in uptake under a change in vaccination policy is modeled as having the largest impact in the first year of the introduction. Phased introduction in different age groups is also possible and therefore we show the budget impact also by age group.

The budget-impact of introducing PCV13 versus the current situation is also shown in Table D.1, using the baseline (retail) price and uptake levels for single dose PCV13 vaccination. It shows that the avoided treatment costs (<€4-6 million for ages 50-84 years), are much lower than the required vaccination costs (>€170 million), resulting in a low (<5%) return on investment, and net costs in excess of €170 million for 50-84 year olds.

Table D.1: Budget impact of PPV23 and PCV13 vaccination versus the current situation. Mean vaccination costs, treatment costs avoided, return on investment and direct net benefits over 5 and 10-year periods. (disc: discounted)

Age group	Avoided treatment costs over 5 years (disc)	Avoided treatment costs over 10 years (disc)	Vaccination costs over 5 years (disc)	Vaccination costs over 10 years (disc)	Return on Investment over 5 years (%)	Return on Investment over 10 years (%)	Direct net benefits over 5 years	Direct net benefits over 10 years
PPV23								
50-64 years	2 058 792	2 635 906	27 950 833	34 767 582	7.4	7.6	-25 892 040	32 131 676
65-74 years	2 795 305	3 738 451	28 522 064	38 348 749	9.8	9.7	-25 726 759	-34 610 298
75-84 years	2 446 399	3 222 201	23 694 979	31 608 894	10.3	10.2	-21 248 580	-28 386 693
85-105 years	0	0	7 100 373	10 120 288	0	0	-7 100 373	-10 120 288
50-84 years	7 300 496	9 596 559	80 167 876	104 725 226	9.1	9.2	-72 867 380	-95 128 667
50-105 years	7 300 496	9 596 559	87 268 249	114 845 514	8.4	8.4	-79 967 753	-105 248 955
PCV13								
50-64 years	1 504 155	2 169 300	60 931 281	75 680 673	2.5	2.9	-59 427 126	-73 511 373
65-74 years	1 941 276	2 876 329	62 782 002	84 319 197	3.1	3.4	-60 840 725	-81 442 868
75-84 years	773 499	1 170 738	52 370 638	69 871 409	1.5	1.7	-51 597 139	-68 700 671
85-105 years	0	0	15 796 465	22 514 983	0	0	-15 796 465	-22 514 983
50-84 years	4 218 930	6 216 367	176 083 921	229 871 279	2.4	2.7	-171 864 991	-223 654 912
50-105 years	4 218 930	6 216 367	191 880 386	252 386 261	2.2	2.5	-187 661 456	-246 169 894

Appendix E

Parameter values and distributions

This supplement presents a summary of all input data used for the economic evaluation. We start with a general overview of the model assumptions and specifications. We list all parameter values and distributions to account for parameter uncertainty using Monte Carlo sampling together with uni- and multivariate sensitivity analysis.

A static age-structured multi-cohort model was developed and applied to the Belgian population aged 50 years and more. Single-year age cohorts above 50 years of age were simultaneously followed from the moment of vaccination until death of the last survivor in the youngest cohort. Cohort sizes over time were informed by standard demography, including age-specific all-cause mortality and life expectancy. The vaccine-induced protection for both IPD and non-IPP was affected by the vaccine scenario (PCV13, PPV23 or both) and timing in combination with the applied waning of vaccine-induced protection.

Due to the large uncertainty in terms of efficacy against non-IPP for both vaccines, we analyzed three base cases:

- PPV23 and PCV13 each have fully parameterized baseline efficacy against non-IPP
- only PCV13 has efficacy against non-IPP (i.e. PPV23 is then assumed to have 0% efficacy against non-IPP)
- both PPV23 and PCV13 have no efficacy against non-IPP.

A serotype change module was used to simulate the impact of childhood vaccination (herd immunity or indirect effects) and trends in serotype distribution in adults. We used a correction factor to account for the decay in PCV13 type incidence per year and for non-PCV13 type incidence increases. We applied the same correction factor for invasive and non-invasive disease types, as the few available data did not suggest different indirect effects. In view of the 2015-2016 change to infant PCV10, also scenarios in which there is a relapse in incidence of "PCV13 non-PCV10" serotypes were explored.

The vaccination coverage determines together with the vaccine efficacy and serotype evolution the population susceptible to acquire invasive or non-invasive pneumococcal disease for each cohort, at each age in years. On these people, we applied age- and serotype-specific yearly incidence rates of the different disease categories. Possible long-term consequences of meningitis (hearing loss or neurological sequelae) were also taken into account. All costs are expressed in euro, and considered from the year 2015.

Table E.1: Characteristics of the two pneumococcal vaccines indicated in the elderly

Characteristics	**23-valent polysaccharide vaccine or PPV23**	**13-valent conjugate vaccine or PCV13**
Commercial name, manufacturer	Pneumovax 23, Sanofi Pasteur MSD	Prevenar 13, Pfizer
Indications authorized in adults according to the European Medicines Agency label in 2015	Prevention of pneumococcal infections due to vaccine serotypes in subjects $\geqslant$2 years of age presenting an increased risk of mortality and morbidity due to pneumococcal infections	Active immunisation for the prevention of invasive disease and pneumonia caused by Streptococcus pneumoniae in adults $\geqslant$18 years of age and the elderly
Serotypes included (bold: serotype not in the other vaccine)	1, **2**, 3, 4, 5, 6B, 7F, **8, 9N** 9V, **10A, 11A, 12F**, 14, **15B, 17F**, 18C, 19A, 19F, **20, 22F**, 23F, **33F**	1, 3, 4, 5, **6A**, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F
Pneumococcal serotype coverage in Belgium in $\geqslant$65 years of age, last estimates for 2015 (based on NRC, see Table E.10)	66% of all IPD	25% of all IPD
Retail price in Belgium[6]	€28.40 per dose	€74.55 per dose
Recommended schedule in Belgium for adults 19-85 years of age with high risk of pneumococcal infection[7].	Primovaccination PCV13 followed by PPV23 after minimum 8 weeks. Those previously vaccinated with PPV23: one PCV13 vaccination, at least 1 year after the last PPV23 dose. Re-vaccination with PPV23 every 5 years	
Recommended schedule in Belgium for adults 50-85 years of age with comorbidity, and healthy adults 65-85 years of age in Belgium[7].	Primovaccination PCV13 followed by PPV23 after minimum 8 weeks. Those previously vaccinated with PPV23: one PCV13 vaccination, at least 1 year after the last PPV23 dose. Booster: to be evaluated, based on supplementary data and the epidemiology after 5 years.	
Recommended schedule in Belgium for adults >85 years of age[7].	There is currently limited data on the effect of pneumococcal vaccination above 85 years of age. On an individual basis, taking into account the risk of pneumococcal infection and the evaluation of the immune response to the vaccine, the clinician may vaccinate a person above 85 years according to the recommended schedule (as above).	

Table E.2: General overview of assumptions and model input parameter values: Vaccination Parameters

Parameter	**Values and distribution**	**Source/Reference**
Current vaccine uptake	Varying from 1% to 20% by age group	Health Interview Survey data[8]
Targeted vaccine uptake	See Table E.6	Targets sets in collaboration with panel of experts of the Belgian National Health Council
Vaccine efficacy (by age) and immunity waning of PCV13	See Table E.7 and E.8	CAPITA[9], Frenck et al[10], Van Werkhoven et al[11]
Vaccine efficacy and immunity waning of PPV23	See Table E.7 and E.9.	Andrews et al[12], Gutierrez et al[13], Ochoa-Gondar et al.[14], Vila-Corcoles et al.[15].
Cost of vaccine administration	€11.7 (half a GP visit or €23.32/2)	Assumption based on expert panel
Cost per PCV13 dose	€74.55 current retail price, reduced prices explored in sensitivity analyses (25% stepwise reductions)	Belgian centre for pharmacotherapeutic information[6]
Cost per PPV23 dose	€28.46 (2015 retail price), reduced prices explored in sensitivity analyses	Belgian centre for pharmacotherapeutic information[6]

Table E.3: General overview of assumptions and model input parameter values: Epidemiological and demographical parameters

Parameter	Values and distribution	Source/Reference
Size target group	Non-random, 2015	Eurostat 2015 population data
Vaccine serotype coverage: IPD	See Table E.10: PCV13 25%; PPV23 66%	NRC 2015 data for serogroups, van der Linden et al.[16] for serotype distribution within vaccine serogroups.
Vaccine serotype coverage: non-IPP	See Table E.11: PCV13 25% ; PPV23 51%	Benfield et al.[17]
Incidence of outpatient pneumococcal disease (non-invasive)	Outpatient all-cause pneumonia incidence, outpatient CAP attributable to pneumococcal infections: 10.5% (95%CI 7.7-13.2). See Table E.12 for estimated incidence of outpatient pneumococcal pneumonia.	INTEGO 2013 R81 for incidence of all-cause pneumonia. Proportion of outpatient CAP due to pneumococcus: pooled estimate from Capelastegui et al and Holm et al[18,19]
Incidence of hospitalised invasive pneumococcal disease	See Table E.13. All IPD assumed to be hospitalized	National Reference Centre (NRC), 2015, and Verhaeghen et al for the distribution of clinical syndromes[20].
Incidence of hospitalised non-invasive pneumococcal pneumonia	Proportion of hospitalised adult pneumococcal CAP that is non-invasive: 82.7% (95%CI 80-86), based on IPD incidence data from Table E.13.	NRC for IPD incidence data. Pooled estimate of four studies for the proportion of hospitalised adult pneumococcal CAP that is non-invasive[21,14,22,23]
Proportion of long term consequences of meningitis	Sequelae in 25.7% of meningitis survivors, assuming 12.9% hearing loss and 12.9% other neurological sequelae. In sensitivity analysis, we assume 20% hearing loss and 22% other neurological sequelae.	Jit[24], Table E.19, Worsoe et al[25] and Ostergaard et al[26]
Case fatality ratio of IPD	See Table E.14	Based on MZG/RHM deaths during hospitalisations, in IPD cases matched between NRC and MZG/RHM
Case fatality ratio (CFR) in outpatient pneumonia	1.7% for all ages (mean age study=74 years) / Sampled from beta distribution	Vila Corcoles et al 2009[27]
Ratio CFR invasive versus non-invasive pneumonia	Adjusted hazard ratio for invasive versus non-invasive pneumonia 2.8 (1.6 - 5.1). Sampled from log-normal distribution	Capelastegui et al 2014[28].
Indirect effect of PCV infant vaccination on PCV13 serotype incidence	Yearly decline of 16% (base case). see Table E.15 for sensitivity analyses.	SPIDNET 2010-15 analysis[29]
Proportion of serotype replacement due to infant vaccination	Yearly compensation of 76.3% of the PCV13 decline (proportion of the PCV13 decline that is compensated by the non-PCV13 serotype increases). Scenarios for sensitivity analyses: Table E.15	SPIDNET 2010-15 analysis[29]
Life expectancy	Belgian national institute of statistics (2014 last available year)	http://statbel.fgov.be table: "sterfte_leven"
Background mortality	Belgian national institute of statistics (2014 last available year)	http://statbel.fgov.be table: "sterfte_leven"

Table E.4: General overview of assumptions and model input parameter values: Costs of treatment

Parameter	Values and distribution	Source/Reference
Hospitalisation cost	Table E.16	MZG/RHM linked with NRC
Out of hospital cost of outpatient pneumonia episodes	€80.9 per outpatient episode. Sensitivity analysis: €104.2 (adding a 2nd GP visit)	Derived from EU project GRACE,[30]
Cost of long term consequences of meningitis	Hearing loss: Average €11 619 / 1st year and €1498 / year in following years. Neurological sequelae: €35 000 /year	KCE report n231[31]

Table E.5: General overview of assumptions and model input parameter values: QALY utilities and discounting

Parameter	Values and distribution	Source/Reference
QALY loss for hospitalised cases	Table E.17, PNEUMOCOST SURVEY France, uncertainty by bootstrapping, taking up QALY loss until 12 months after hospitalisation	PNEUMOCOST SURVEY France, personal communication of Gerard de Pouvourville, ESSEC, 2016[32]
QALY loss for non-hospitalised pneumonia	Utility value QoL: 0.508 (0.442 - 0.575) sampled from normal distribution, applied during 8.5 days	Galante et al.[32]
QALY loss long term consequences of meningitis	Utility weight for hearing loss: 0.635 (lifelong). Utility weight for neurological sequelae: 0.319 (lifelong). Sampled from normal distribution	Galante et al[32]
UK population norms to use with Galante et al (average age: 31 years) disease-specific UK-derived utilities	0.93	Age group 25-35 years from Kind et al.[33]
Discount rate for costs	0.03	Cleemput et al[34]
Discount rate for health outcomes (life years, QALYs)	0.015	Cleemput et al[34]

Table E.6: Vaccination strategies defined by vaccine choice, schedule and uptake in different age groups.

Scenario	50-64 years	55-74 years	75-84 years	85-105 years
Current situation (yearly means of the 2004, 2008 and 2013 five year accumulated uptake)	0.79% PPV23	2.46% PPV23	3.01% PPV23	2.48% PPV23
PPV23 (1)	25% PPV23	50% PPV23	60% PPV23	40% PPV23
PCV13 (2)	25% PCV13	50% PCV13	60% PCV13	40% PCV13
PCV13 + PPV23 (3)	(1) + (2)	(1) + (2)	(1) + (2)	(1) + (2)
PPV23 + revaccination	(1) + 15% PPV23 after 5 year	(1) + 25% PPV23 after 5 year	(1) + 25% PPV23 after 5 year	(1) + 20% PPV23 after 5 year
PVC13 + revaccination	(2) + 15% PPV23 after 5 year	(2) + 25% PPV23 after 5 year	(2) + 25% PPV23 after 5 year	(2) + 20% PPV23 after 5 year
PCV13 + PPV23 + revaccination	(3) + 15% PPV23 after 5 year	(3) + 25% PPV23 after 5 year	(3) + 25% PPV23 after 5 year	(3) + 20% PPV23 after 5 year

Table E.7: PCV13 and PPV23 efficacy by age and IPD/non-IPP: baseline assumptions and sensitivity analysis[12,13,14,15,9,10,11]. Parameter mean and distribution are shown.

	PCV13	PPV23	Sensitivity analysis: increased PPV23 efficacy	Sensitivity analysis: Age-specific PCV13 efficacy
IPD				
50-84 years	75.8% (47 to 90)	56% (40 to 68)	82% (69-90)	Scale to the hazard rate $f_{HR} = 1.058$ (1.008 to 1.111) per year of age
⩾85 years	0%	0%	0%	0%
non-IPP				
50-79 years	41.1% (12.7%-62%)	30.8% (22%-37%)	43.1% (31%-52%)	Scale to the hazard rate $f_{HR} = 1.058$ (1.008 to 1.111) per year of age
⩾80 years	0%	0%	0%	0%

Table E.8: Baseline and sensitivity PCV13 vaccine efficacy waning assumptions for 50-84 year olds based on a logistic waning using t_{50}: the time at which the current vaccine protection is reduced to 50% of initial vaccine efficacy and waning rate [12,13,14,15,9,10,11].

Scenario	Period of fixed vaccine protection	50% point (t_{50})	Waning rate (k)
Base case	5	10 years	0.75
Min. scenario	4	6 years	0.75
Max. scenario	9	15 years	0.75
5 years only	5	-	-

Table E.9: Baseline and sensitivity PPV23 vaccine efficacy waning assumptions for 50-84 year olds based on a exponential waning using t_{50}: the time at which the current vaccine protection is reduced to 50% of initial vaccine efficacy.

Scenario	Period of fixed vaccine protection	50% point (t_{50})
Base case	2	1.5 years
2 years only	2	-
5 years only	5	-

Table E.10: Vaccine serogroups and serotypes in IPD cases (2015) among Belgian adults above 18 years of age, based on serogroup distribution reported by the Belgium National Reference Centre and serotype distribution from Van der Linden et al.[16] -: non applicable; *: serogroups from which at least one serotype is included in the vaccine.

Vaccines	Serogroups* (observed counts)	Non-vaccine serotypes	Vaccine serotypes (estimated counts)
PCV13 and PPV23 (serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F)	37.4% (445)	13%	24.4% (241.9)
PPV23 only (serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F and 33F)	45.3% (552)	3.5%	41.8% (415.2)
PCV13 only (serotype 6A)	3.4% (38)	2.4%	1.0% (9.5)
All PCV13	40.8% (483)	-	25.3% (251.4)
All PPV23	82.7% (997)	-	66.2% (657.2)
No vaccine	13.9% (174)	-	32.9% (326.4)

Table E.11: Serotype distribution in IPD and non-invasive CAP among adults ($\geqslant$50 years) estimated in Belgium in 2015. *: counts are estimated by applying the van der Linden[16] serotype distribution to 2015 NRC serogroup counts; **: Based on Benfield et al 2013[17] extrapolated to 2015 based on annual serotype changes in IPD from SPIDNET network; CAP: community acquired pneumonia; IPD: Invasive pneumococcal disease; NRC: National Reference Centre.

Serotype groups	Proportion of vaccine serotypes in IPD in Belgium, NRC (estimated counts)*	Proportion of vaccine serotypes in non-invasive CAP (counts)**
PCV13 and PPV23 (serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F)	24.4% (241.9)	24.4% (64)
PPV23 only (serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F and 33F)	41.8% (415.2)	26.6% (69)
PCV13 only (serotype 6A)	1.0% (9.5)	0.3% (1)
All PCV13 serotypes	25.3% (251.4)	24.7% (64)
All PPV23 serotypes	66.2% (657.2)	51.1% (133)
Non-vaccine serotypes	32.9% (326.4)	48.7% (127)
Total	100% (993)	100% (260)

Table E.12: Incidence of outpatient all-cause and pneumococcal pneumonia per 100 000 persons (INTEGO 2013 R81 codes and[18,19]). The estimated practice population is used as denominator. The yearly incidence rate of pneumonia is sampled from a beta(cases, denominator-cases) distribution to take uncertainty into account.

Age group	Cases (2013)	Denominator (Practice population 2013)	All cause pneumonia (INTEGO)	Estimated pneumococcal pneumonia incidence
50-64 years	159	26555	598.8	57.0
65-74 years	75	11157	672.2	64.0
75-84 years	84	8325	1009.0	96.1
⩾85 years	63	4187	1504.7	143.3

Table E.13: Incidence of invasive pneumococcal disease (IPD) per 100 000 inhabitants in Belgium, 2015 National Reference Centre data corrected for underreporting[20,21,14,22,23]. * bacteraemia without focus, septicaemia, septic arthritis, peritonitis etc.

Age group	Meningitis	Invasive pneumonia	Other IPD*	Total IPD
50-64 years	1.3	12.4	1.2	14.9
65-74 years	1.1	22.1	2.2	25.5
75-84 years	1.6	32.0	3.2	36.8
⩾85 years	3.6	69.6	7.0	80.2

Table E.14: Case fatality ratio of pneumococcal meningitis, pneumococcal septicemia and pneumococcal pneumonia as primary diagnosis, cases matched in MKG (ICD9) and NRC, 2007-12

	Meningitis			Septicaemia			Pneumonia		
Age group	Cases	Deaths	CFR (%)	Cases	Deaths	CFR (%)	Cases	Deaths	CFR (%)
50-64 years	68	9	13.2	368	61	16.6	509	31	6.1
65-74 years	43	5	11.6	298	49	16.4	404	40	9.9
75-84 years	18	4	22.2	348	64	18.4	404	58	14.4
⩾85 years	8	4	50.0	223	50	22.4	255	57	22.4

Table E.15: Serotype change scenarios informed by SPIDNET 2010-2015 data[29]. The serotype replacement is calculated as the relative non-PCV13 serotype increase divided by the relative decline of PCV13 serotypes. Based on SPIDNET data, we assumed a yearly increase of 4% of non-PCV13 types (that represented 75.3% of 2015 IPD incidence in Belgium) and an average decline of 16% of PCV13 types (24.7% of 2015 Belgian IPD incidence). This results in a yearly PCV13 serotype replacement of (4% * 75.3%) / (16% * 24.7%) = 76.3%.

Scenario tag	Scenario description	PCV13 serotype decline (per year)	Replacement (per year)	Relapse
Baseline scenario	Average of SPIDNET of changes of non-PCV7 PCV13 serotypes	-16%	76.3%	no
Min. scenario	Rounded minimum yearly decline SPIDNET data of changes of non-PCV7 PCV13 serotypes	-10%	76.3%	no
Max. scenario	Rounded maximum yearly decline SPIDNET data of changes of non-PCV7 PCV13 serotypes	-20%	76.3%	no
Quick relapse	PCV13 serotype incidence returns to its 2015 value within 7 years	-16%	0%	With logistic curve: (t50%=5years, k=1)
Slow relapse	PCV13 serotype incidence returns to its 2015 value within 15 years	-16%	0%	With logistic curve: (t50%=10 years, k=0.5)

Table E.16: Mean costs of pneumococcal disease, per clinical syndrome (ICD9 primary diagnosis) in cases matched in MZG/RHM and NRC, 2007-12.

Age group	Meningitis	Septicemia	Pneumonia
50-64 years	€7686	€8114	€5669
65-74 years	€8900	€6317	€5909
75-84 years	€9103	€5003	€1679
⩾85 years	€6973	€3137	€3466

Table E.17: QALY loss estimates of surviving hospitalized pneumococcal pneumonia patients (PNEUMOCOST-survey), up to 12 months, by age group and disease type. The QALY loss was negative for a minority of patients, which is expected given that the Quality of Life scores are compared to the population norms (from France) for an average person of the same age and risk group. Some patients in the study accumulated more (fractional) QALYs over a year than that the average person of the same age and risk group experiences.

Age group	Disease	Average QALY loss (over 1 year)	Minimum QALY loss (over 1 year)	Maximum QALY loss (over 1 year)	Number of patients
0-64 years	Non-invasive	0.0491	-0.3283	0.9692	69
0-64 years	Invasive	0.0203	-0.3288	0.5244	36
⩾65 years	Non-invasive	0.0679	-0.2713	0.8336	21
⩾65 years	Invasive	0.1741	-0.2768	0.6710	28

Table E.18: Age-specific hospitalizations rate per 100 000 population for Pneumococcal Disease related ICD9 codes in MZG/RHM (Belgium 2013, first or secondary diagnostic field).

Age group	Pneumococcal meningitis (ICD9 320.1)	Pneumococcal pneumonia (ICD9 481)	Pneumococcal septicaemia (ICD9 038.2)
50-64 years	0.7	13.8	4.4
65-74 years	1.6	41.9	15.0
75-84 years	1.3	60.8	19.8
⩾85 years	0.0	88.2	43.6

Table E.19: Frequency of sequelae in pneumococcal meningitis, per type. The proportion of survivors with each type of hearing loss is calculated by applying the proportion on all cases with audiometry to the total cases with hearing loss. *: including hearing loss. -: non applicable

	Ostergaard 2005[26]	**Kastenbauer 2003[35]**	**Weisfelt 2006[36]**	**Worsoe 2010[25]**	**Aubertin 2006[37]**
Country	Denmark	Germany	The Netherlands	Denmark	France
Study period	1999-2000	1984-2002	1998-2002	1999-2003	2001-2003
Age group (mean)	>16 years (61 years)	>16 years (50 years)	Adults (58 years)	>18 years	>18 years (56 years)
Number adult survivors	96	66	243	144	105 (ICU)
Any neurological sequelae*	-	-	30%	-	34.3%
Hearing loss >30dB	No definition	25.8%	21.8%	20.0%	No definition
Unilateral hearing loss >30dB	-	9.1%	6.8%	-	-
Bilateral hearing loss >30dB	-	16.7%	15.0%	-	-
Hearing loss 30-70 dB	-	16.7%	11.3%	12.5%	-
Hearing loss 70-90db	-	4.5%	3.7%	>70 dB: 10.4%	-
Hearing loss >90db	-	4.5%	6.8%	>70 dB: 10.4%	-
Other: neurological	22.0%	unclear	unclear (multiple sequelae)	-	-
Other: cranial nerve palsies	-	4.6%	28%	-	-
Other: hemiparesis	-	-	7%	-	8.6%
Other: focal cerebral deficit	-	-	11%	-	-

Table E.20: Case fatality ratio of pneumococcal disease (%) estimated in Belgium in 2015, by outcome. CAP: Community acquired pneumonia; IPD: Invasive pneumococcal disease, including invasive pneumonia; *: hospital deaths in cases matched in NRC and MZG/RHM; **: by applying a hazard ratio of 2.8 in invasive pneumococcal CAP vs. non-invasive;

Age group	**Inpatient IPD***	**Inpatient non-invasive pneumococcal CAP****	**Outpatient pneumococcal CAP[27]**
50-64 years	10.7%	2.2%	1.7%
65-74 years	12.6%	3.5%	1.7%
75-84 years	16.4%	5.1%	1.7%
⩾85 years	22.8%	8.0%	1.7%

Table E.21: Cost estimates for meningitis sequelae.

Parameter	Value	Source/Reference
Proportion of hearing loss in meningitis survivors	12.9% in base case and 20% in sensitivity analysis	Jit et al.[24] and Worsoe et al.[25]
Proportion of hearing loss requiring hearing aid (>30dB and <90dB)	75%	Kastenbauer and Weisfelt[35,36]
Proportion of hearing loss requiring cochlear implant (⩾90dB)	25%	Kastenbauer and Weisfelt[35,36]
First year cost per hearing aid	€529	Hanquet et al[31]
Cost for every following year per hearing aid	€339	Hanquet et al[31]
First year cost per cochlear implant	€26,298	Hanquet et al[31]
Cost for every following year per cochlear implant	€2577	Hanquet et al[31]
Number of implants needed per hearing loss patient (average number of ears affected)	5/3	Kastenbauer and Weisfelt[35,36]
Average cost of treatment of hearing loss, per patient, first year	€11 618.75	Calculated from the respective proportion cost of hearing aid and cochlear implant.
Average cost of treatment of hearing loss, per patient, in the following years	€1497.5	Calculated from the respective proportion cost of hearing aid and cochlear implant.
Proportion other neurological sequelae in meningitis survivors	12.9% in base case and 22% in sensitivity analysis	Jit et al[24] and Ostergaard et al.[26]
Average cost of treatment for neurological sequelae, per year	€35,000	Beutels et al.[38]

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